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Final Report Phase II

RESEARCH OPPORTUNITIES IN SPACE MOTION SICKNESS

February 1983

Prepared for

THE LIFE SCIENCES DIVISION
OFFICE OF SPACE SCIENCE AND APPLICATIONS
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FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY
FASEB

LIFE SCIENCES RESEARCH OFFICE
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Edited by
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was developed for the National Aeronautics and Space Administration (NASA) in accordance with the provisions of Contract NASW 3616. It was prepared and edited by John M. Talbot, M.D., Senior Medical Consultant, LSRO, with the advice and assistance of Herbert L. Borison, Ph.D., Professor of Pharmacology, Dartmouth Medical School.

The LSRO acknowledges the contributions of the investigators and consultants who assisted with this study. The report reflects the opinions expressed by members of an ad hoc study group that met at the Federation on September 13 and 14, 1982. The study participants reviewed a draft of the report and their various viewpoints were incorporated into the final report. The study participants and LSRO accept responsibility for the accuracy of the report; however, the naming of these individuals in Section VIII does not imply that they specifically endorse each study conclusion.

The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to NASA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

February 28, 1983
(date)

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

SUMMARY

An important part of NASA's Biomedical Research Program focuses on space motion sickness, a disorder whose adverse effects on the well-being, effectiveness, and safety of spacecrew members justify extraordinary efforts to resolve the problem.

NASA astronauts and flight surgeons did not report any instance of frank space sickness during the Mercury and Gemini missions; however, in retrospect, the anorexia and diminished food intakes noted by some of the Gemini crews were suggestive of early manifestations of space sickness. The disorder was reported in the crews of Apollo 8, 9, 15, and 17, and five of the nine crewmen who participated in the three, three-man Skylab missions experienced some degree of space sickness while in the command module or in the workshop. Soviet cosmonauts' experiences with the disorder have been closely similar to those of the astronauts, and the combined frequency of U.S. and U.S.S.R. instances of space sickness, on a per crew member basis, approximates 50%.

Space sickness is likely to occur and impair crew well-being and performance during the initial 2-5 days of a mission, during which habituation takes place, resulting in tolerance for the causative stimuli. Thus, space sickness is highly significant during the first few days of spaceflight, a factor of some concern in all manned spaceflights, but especially in missions of relatively short duration such as those in the Space Shuttle program.

Space sickness is generally regarded as a variant of the more common type of motion sickness. However, the provocative stimuli must be somewhat modified from those that cause ordinary motion sickness because the spacecraft and astronauts in orbital flight are in continuous free fall and are, therefore, in a state of weightlessness. Moreover, the accelerations resulting from motions of the spacecraft during stable flight are described as trivial. Head and body movements in combination with the influence of weightlessness are thought to be the main sources of the stimuli that induce space sickness.

Development of a widely accepted, scientific definition of space sickness is hampered by a serious lack of data on the precise causal stimulus or stimuli and on the basic biologic mechanisms involved in the genesis of, and habituation to, the disorder. The same may be said for ordinary motion sickness except that for it, the initiating stimuli have been reasonably well documented. As a result of critical gaps in knowledge, research continues to be formulated on the basis of theory and hypothesis. The most popular theories include sensory mismatch, sensory conflict, and sensory overstimulation and overflow. While these theories appear basically logical, they fail to identify the precise, adequate stimulus

for space sickness, nor do they explain fundamental mechanisms involved in translating the cause into such responses as nausea, vomiting, and habituation.

With the exception of drugs, promising approaches toward prevention and control of space sickness have not led to practical countermeasures; for example, means of identifying resistant individuals and vestibular adaptation training. Autogenic feedback (biofeedback) training of aircrew members appears to be a practical method of dealing with air sickness, but whether it may be practical for astronauts remains to be demonstrated. Thus, at present, NASA uses prophylactic and therapeutic anti-motion sickness drugs, which have proved useful during some, but decidedly not all, space missions. Unfortunately, their potential effectiveness for preventing or controlling space sickness cannot, as yet, be predicted on the basis of preflight tests. Nevertheless, the search for improved anti-motion sickness drugs should continue as a key element in NASA's research program.

Aside from a possible fortuitous breakthrough in countermeasures, satisfactory solution to the problem of space sickness will depend upon identification of its cause or causes as well as discovery and elaboration of the basic mechanisms that mediate the syndrome and the associated processes of habituation. Key questions include whether the vestibular apparatus is indispensable to the space sickness response, and which factors determine individual susceptibility or tolerance.

Major, essential data are unavailable for explaining the train of events that starts with exposure to the causal stimulus, moves into the stage of acute symptomatic response, initiates concomitant processes of adaptation and habituation, and, postflight, reverses itself during reaccommodation to the terrestrial environment. Much greater emphasis should be placed on generating research in those disciplines, in addition to vestibular physiology, that offer promising approaches such as the anatomy, biochemistry, pharmacology, and endocrinology of the reflex circuits involved and the use of some of the more recent investigative methods of neuroscience. Such emphasis should aid in broadening the research program and expediting discovery of such essentials as the key neuronal circuits involved, their associated receptors, transmitters, and modulators, and the determination of the indispensible anatomic and humoral elements in the reflex pathways of space and motion sickness, and their biologic mechanisms.

This report contains a summary review of space and motion sickness, comment on the current and projected NASA research program, and the conclusions and suggestions of the ad hoc Working Group. The frame of reference for the report is ground-based research; however, members of the Working Group acknowledge the extreme importance of acquiring certain critical data from inflight studies. Thus, there is no intended implication of detracting from the importance of current and future plans for inflight experiments.

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I. INTRODUCTION

Manned space missions have been spectacular in their accomplishments and reassuring in their demonstration of an absence of permanent untoward biomedical effects. Indeed, no manned mission, once launched, has had to be aborted because of human factors. However, it is well known that exposure to the space environment does result in a number of unusual biomedical effects. These have been described by Berry (1974), Calvin and Gazenko (1975), Gazenko et al. (1981), Genin and Egorov (1981), and Johnston and Dietlein (1977).

Space motion sickness is the only adverse effect of space flight that has significantly impaired crew effectiveness during flight. It is typically reported during the initial 1-5 days in orbit, and it appears to be related to moving about and attemping to perform complex tasks in the spacecraft (Daunton, 1982). Data from the Apollo and Skylab programs indicate the onset of symptoms occasionally occurred as early as 2 hours after launch, and the manifestions disappeared within 2-5 days post-launch (Graybiel et al., 1977). The reported combined prevalence of the disorder in U.S. and Soviet manned space flights approximates 50 percent of personnel in all flights since the Gemini program (Cramer, 1982). The manifestations have ranged from mild feelings of gastric awareness and malaise to moderately severe nausea and vomiting (Graybiel, 1980; Homick, 1979; Nicogossian and Pool, 1982; Pool et al., 1982; Yakovleva et al., 1981). Associated phenomena have sometimes included spatial illusions and a group of manifestations called the sopite syndrome, which is characterized by yawning, somnolence, indifference toward mental and physical work, and nonparticipation in group activities (Graybiel and Knepton, 1976). This is not unlike the behavior associated with nausea and vomiting from other causes unrelated to motion sickness; for example, radiation sickness.

The causation of space sickness is not well defined, and a practical understanding of its nature, which is urgently needed for operational purposes, is further clouded by lack of exact information on its occurrence and lack of data on the biologic mechanisms involved in its genesis. The term itself may be somewhat misleading in that the motion component, as it may occur in a spacecraft, requires improved definition. For example, the passive accelerations resulting from motions of the spacecraft in stable flight have been described as trivial (Graybiel, 1975); on the other hand, accelerations resulting from movements of head and body during flight can be large and appear to contribute to the induction of the syndrome (Graybiel et al., 1977; Matsnev and Homick, 1981), but these would not ordinarily induce symptoms on the ground. To avoid confusion with "motion sickness" as a terrestrial phenomenon, the emetic syndrome that occurs in space flight is frequently referred to as "space sickness."

Among the approaches that have been investigated for managing the problem are prophylactic and therapeutic medications, preflight vestibular adaptation training, identification of susceptible and resistant individuals, restriction of head and body movements, and autogenic feedback (biofeedback) training. With the partial exception of drugs, none of these efforts has led to practical applications for space flight. Thus, NASA has relied mainly on the use of anti-motion sickness drugs, which have been reported to be effective in some cases for prevention or treatment, but not an "ideal" solution (Graybiel et al., 1977).

The substantial evidence that space sickness may commence as early as 2-3 hours after launch and is prevalent during the first 5 days of space flight is particularly relevant to the U.S. Space Transportation System (Shuttle) program in which 4 days represent between one-third to one-half of the time duration of each projected mission.

There is considerable anecdotal information available on space sickness. Additional data on its cause and mechanisms, adaptation and habituation, individual susceptibility, and practical methods of prevention and control are needed. To aid in its future research program planning, NASA requested that the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) review the subject of space sickness, including available knowledge, the current and projected NASA program of ground-based research, data that are critically needed, and types of investigations that should be considered in NASA's future program of ground-based research. This has been done with the assistance of an ad hoc group of prominent scientists, whose names are listed in Section VIII.

II. OBJECTIVES AND SCOPE OF THE STUDY

The objectives of the LSRO study of space sickness are:

(1) to review extant knowledge of the subject and identify significant gaps in essential knowledge; and

(2) to examine NASA's current and projected research program and formulate suggestions to NASA for future research.

The main sources of information for the study were (a) the members of the ad hoc Working Group; (b) the scientific and technical literature; (c) unpublished data from the U.S. and Soviet space programs; and (d) the NASA Research and Technology Objectives and Plans (RTOPs) and Research and Technology Resumes (RTRs) on space sickness and related biomedical problems of space flight.

III. A SYNOPSIS OF SPACE AND MOTION SICKNESS

A widely accepted, scientific definition of motion sickness does not exist, primarily because of a lack of understanding of its etiology and mechanisms. However, its signs and symptoms have been well documented as have the types of motions and other stimuli associated with the syndrome. Chinn and Smith (1955), Graybiel (1973; 1975), Money (1970), Reason and Brand (1975), and Tyler and Bard (1949), have prepared excellent reviews of motion sickness. Prevailing concepts of the physiology and pharmacology of vomiting are reviewed by Borison and Wang (1953).

Knowledge of the biologic mechanisms of motion sickness and its spaceflight version is insufficient to allow precise control via such potentially useful means as preselection of resistant individuals and preflight habituation* to unconventional motion stimuli (Homick, 1979). Anti-motion sickness drugs offer a partial, but not an optimal, remedy for prevention and control of symptoms.

Two hypotheses have generated much of the current basic research on space sickness: the more widely acknowledged sensory conflict or sensory mismatch hypothesis (Reason, 1969; 1978) and the labyrinth fluid imbalance model, based on the fluid shift concept (Barrett and Lokhandwala, 1981; Parker, 1977; Tonndorf, 1982; Wolfe et al., 1981). However, despite substantial efforts to elucidate the maladaptation phenomenon which occurs upon exposure to the weightless state, the mechanisms underlying space sickness remain largely unexplained.

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* In this report, "habituation" is used, instead of "adaptation" to indicate the decline in response with repeated exposures to a novel stimulus (Collins, 1974; Guedry, 1974; Jäger and Henn, 1981; Kandel, 1977). Habituation is said to occur in the central nervous system as distinct from sensory adaptation, which takes place in the sensory end organ. (For example, see Taglietti et al. 1977). In a relatively narrow sense, sensory adaptation may be regarded as a temporary decline in response that can occur during the first, steady exposure to a novel stimulus. Habituation can be described as specific for a particular stimulus and as a relatively long-lasting phenomenon as contrasted with such temporary effects as fatigue and sensory adaptation (Thorpe, 1974). However, many authors prefer the term, adaptation, to indicate the process whereby subjects become tolerant to nauseogenic motion stimuli following repeated exposures.

A. DEFINITION AND NATURE OF MOTION AND SPACE SICKNESS

Space sickness is generally regarded as a variant of the more common types of motion sickness (Daunton, 1982; National Aeronautics and Space Administration, 1982). It exhibits the cardinal signs and symptoms of ordinary motion sickness (Benson, 1977; Graybiel et al., 1977), and responds to anti-motion sickness drugs favorably in some instances. On occasion, it has been sufficiently disturbing to require temporary reduction in the scheduled activities of the astronauts (Graybiel et al., 1977), and has caused major concern of both U.S. and Soviet space authorities (Heaney, 1974; National Aeronautics and Space Administration, 1982; Soffen and Gazenko, 1981). After about 2-5 days in orbital flight, during which a process of habituation takes place, most individuals become immune to further space sickness during a given mission. However, symptoms of space sickness persisted "for a long time" during the adaptation period of one crew member in the 96-day Salyut-6 mission, and the commander of the 140-day Salyut-6 mission experienced "mild vestibular discomfort" during head and trunk movements on mission day 130 (Yakovleva et al., 1981). In the first few days immediately postflight, a recurrence of signs and symptoms is not uncommon when ordinary motion stimuli are introduced by head and body movements and changing from the supine to the vertical posture (Homick 1979; Yakovleva et al., 1981).

The following manifestations of motion sickness were listed by Chinn and Smith (1955): anorexia, drowsiness, pallor, epigastric awareness, malaise, cold sweat, nausea, vomiting, and retching. In addition, salivation, headache, increased intestinal peristalsis, fatigue, and mental depression had been observed. Chinn and Smith (1955) pointed to the marked variability among subjects, of the sequence, number, and intensity of symptoms, which clouded the issue of identifying firm criteria of motion sickness. Graybiel (1969) considered that the syndrome represented "epiphenomena" resulting from receipt of unnatural stimuli by vestibular organs and in higher cortical centers not normally characterized as vestibular receiving areas. Money (1970) described motion sickness as a malady caused by certain kinds of motions and characterized by such signs and symptoms as malaise, pallor, cold sweating, nausea, and vomiting. Motion sickness was considered to be present whenever any of the signs and symptoms was evoked by motion.

The manifestations of space sickness may include mild gastric or epigastric awareness, pallor, cold sweating, salivation, nausea, and vomiting (Matsnev and Homick, 1981; Money, 1970). The sopite syndrome, featuring drowsiness, indifference toward mental and physical activity, weakness, and social withdrawal may predominate in some instances (Graybiel and Knepton, 1976; Matsnev and Homick, 1981).

Experience has shown that space sickness is likely to impair crew performance and well-being during the initial few days of a mission. However, the tolerance of crews to provocative stimuli progressively increases with time in orbit, and after a few days, they are no longer disturbed by head movements or by cross-coupled (Coriolis) stimuli which induced sickness preflight. Thus, space sickness may be highly significant during the first few days of space flight, a factor of some concern in all manned space flights, but especially in missions of relatively short duration such as those contemplated for the Space Shuttle.

B. OCCURRENCE

NASA astronauts and flight surgeons did not report any instance of space sickness during the Mercury and Gemini missions (Table 1); however, the anorexia and diminished caloric intakes noted by some of the Gemini crews were suggestive of early manifestations of space sickness (Dietlein, 1977). Until the Skylab missions (May, 1973), a total of nine American and four Soviet crewmen experienced space sickness as well as other symptoms considered to be of vestibular origin during orbital flight (Graybiel et al., 1977). Individual members of the crews of Apollo 8, 9, 10, 13, 15, and 17 reported some manifestations of space sickness; in missions 10, 15, and 17, the reported symptoms were said to be limited to stomach awareness (Homick and Miller, 1975). Five of the nine crewmen who participated in the three, three-man Skylab missions experienced some degree of sickness while in the command module or in the workshop (Table 1). Parker (1980) noted that 14 of 34 astronauts who participated in the Apollo and Skylab programs experienced space sickness (see Table 2).

In their report on vestibular function of the crews of the 96- and 140-day Salyut missions (MC-I and MC-II), Yakovleva et al. (1981) described "vestibular discomfort" consisting of vertigo and mild nausea in both MC-I crewmen when they moved their heads. The authors noted that the habituation period was characterized by violent but brief (3 days) reactions in the commander and that the flight engineer experienced less marked reactions that persisted for a "long time" during the habituation period. Details of the reported reactions were not presented. Postflight, the commanders of both Soviet expeditions presented, in addition to statokinetic disorders, "marked vestibulovegetative manifestations including vertigo, nausea, and retching, which were particularly intensive when moving the head and changing to the vertical position" (Yakovleva et al., 1981) (see Table 3).

Tolerance to motion varies markedly among individuals and even in the same individual under the influence of different kinds of motion stimuli (Reason and Brand, 1975). Most normal persons can be made motion sick provided the motion stimuli are applied long enough and are of sufficient intensity. The rate of occurrence of

Table 1. Space Sickness During U.S. Manned Space Flight Programs

Program	Number of Crewmen	Incidence of Reported Symptoms
Mercury	6	0
Gemini	20*	0
Apollo	33*	11†
Skylab	9	5
ASTP§	3	0
STS¶	12	6

* Includes 4 crewmen who flew twice during program.
† Includes 1 crewman who experienced symptoms on both of two flights.
§ Joint U.S.-U.S.S.R. Apollo-Soyuz mission.
¶ Space Transportation System/Shuttle Orbiter.

Table 2. Space Sickness*

Probable variant of terrestrial motion sickness

Characterized by:

Inflight

- Onset shortly after beginning to move about in weightlessness
- Symptoms aggravated by movement and persist 2-5 days
- Illusions may be encountered with these movements; spatial disorientation and illusions minimal and of no operational significance
- Nausea, cold sweating, pallor, vomiting
- Crew performance and mission timelines occasionally disrupted
- After adaptation, inflight resistance to motion stimuli is high
- Anti-motion sickness drugs are the only therapy used to date; efficacy has been limited

Postflight

- Isolated symptoms of motion sickness apparently induced by recovery ship motion
- Temporary ataxia and postural dysequilibrium
- No significant illusions or disorientation

Based on Skylab:

- About 50% of crew members will be symptomatic
- Perhaps 15% will be frankly ill
- Incidence appears related to movement within spacecraft
- Medications are useful but not completely effective
- Ground-based tests cannot yet meaningfully predict who will become sick

Experience on STS† missions 1 through 5 was consistent with the above data except that manifestations of the sopite syndrome (Graybiel and Knepton, 1976) appeared to be more prevalent than in prior NASA programs.

* Source: unpublished material from Johnson Space Center workshop on space motion sickness, June 1982, based mainly on experiences of U.S. astronauts.
† Space Transportation System, Shuttle flights.

Table 3. Observations from U.S.S.R. Program*

PREFLIGHT

- "Active" and "passive" vestibular training technics used with all cosmonauts
- 6° Head-down tilt during sleep used as fluid shift conditioning technic
- Ground-based tests do not correlate well with inflight symptoms
- Parabolic flight reasonably good predictor of inflight symptoms

INFLIGHT

- Space sickness experienced by 40-45% of cosmonauts
- Main symptoms are sweating, salivation, dizziness, nausea and vomiting
- In all cases symptoms aggravated by head movements
- Periods of adaptation vary from one to several days
- Many crewmen experienced various illusions of body tilt and visual displacement
- No quantitative vestibular response measurements
- Countermeasures included:
  - Antihistamine anti-motion sickness drug
  - Voluntary restriction of head movements
  - Mechanical devices (elastic cap† and pneumatic waist and thigh cuffs)

POSTFLIGHT

- Motion sickness symptoms (exacerbated by head movements) seen in some crewmen
- Ataxia experienced by most crewmen
- Hypo- and hyper-reflexia of otolith function (ocular counterrolling)
- Increased canal reactivity (cupulogram)
- Tendon hyper-reflexia

* Source: Unpublished material from Johnson Space Center workshop on space motion sickness, June 1982.

† Imparts mechanical load to cervical muscles and restricts head movement.

at least one episode of airsickness in military aviation trainees was reported at 10-18% of student pilots and 66% of student navigators; the "washout" rate was about 1% for pilots and 5% for navigators because of intractable motion sickness (Money, 1970). A striking fact is that many individuals demonstrate high resistance to motion sickness, and, as was noted above, at least 50% of U.S. astronauts have reported no signs or symptoms of space sickness. As has often been stated, one key to solving the problem of motion and space sickness may be to discover the source of tolerance in resistant individuals.

Thus, space sickness is a temporary disorder with manifestations essentially identical with those of ordinary motion sickness, that affects approximately 50% of astronauts, begins as early as 2 hours following launch, and usually disappears after 2-5 days in orbit.

C. CAUSE AND MECHANISMS

Exposure in a vehicle or test apparatus to unconventional types, patterns, and intensities of motion is generally regarded as the precipitating factor in motion sickness. Even motion of the visual surround as perceived, for instance, in viewing a motion picture of Earth and sky taken from a maneuvering aircraft may induce symptoms of motion sickness in immobile, susceptible individuals. Another variant of motion sickness is simulator sickness, which has been observed in individuals following training sessions in ground-based flight simulators (Crosby and Kennedy, 1982).

In space flight, the precipitating factor appears to be motion; that is, movements of the head or body (Graybiel et al., 1977; Matsnev and Homick, 1981). However, the movements that are associated with space sickness include the ordinary movements of head and body that in the normal gravity environment on Earth do not elicit symptoms. With reference to the spacecraft, Graybiel (1975) noted that, except during launch, programmed or unprogrammed maneuvers in orbit, and reentry, the passive, angular accelerations produced by the spacecraft in stable flight are trivial from a physiologic standpoint. However, some U.S. as well as Soviet spacecraft have been known to rotate slowly inflight.

Thus, a key question about the etiology of space sickness is: how does weightlessness influence the occurrence and nature of the disorder? An interesting associated question is: can weightlessness evoke the syndrome in the absence of head and body movements? Most reports indicate that head and body movements are necessary components in the etiology of space sickness (Benson, 1977; Graybiel et al., 1977; Matsnev and Homick, 1981; Yakovleva et al., 1981). Whether immobilization of the head and body during space flight would prevent the disorder has not been scientifically

tested. Nevertheless, the absence of space sickness in the Mercury and Gemini programs has been attributed to the relative immobilization of the astronauts imposed by the confined crew spaces and the wearing of movement-impeding space suits and helmets (Berry, 1973; Dietlein, 1977; Homick, 1979).

Several factors that may bear on the causation of space sickness include the functional adequacy of the vestibular apparatus, integration with other sensory inputs, and possible alterations of sensory and motor programming in the zero-G environment. Money (1970) pointed out that most theories on the nature of motion sickness were in one of two categories: a discord or confusion in sensory inputs, or overstimulation resulting in "spillover" of impulses from centers of equilibration to centers that can generate manifestations of motion sickness. In his view, neither category is convincingly supported by scientific evidence.

Reason (1978) considered that a mismatch between the information received from the spatial senses and that in the neural store from past experience led to symptoms of motion sickness. In other words, a maladaptation occurs when the neural store is at variance with the prevailing sensory input resulting from exposure to an unnatural motion environment. An essential component of the theory is an intact, functional vestibular system. In this regard, it is noteworthy that people who lack a functional vestibular apparatus do not get motion sick. Whether they are susceptible to space sickness is unknown.

Overstimulation of the vestibular end organ by exposure to vigorous motions, resulting in an excessive response in the vestibular nuclei with "spillover" or "radiation" into adjacent neural centers has been suggested as a pathogenetic mechanism for motion sickness (Brooks, 1939; Desnoes, 1926; Gillingham, 1965; Steele, 1963). However, this hypothesis does not account for the absence of sickness during lively horseback riding, for example. According to Graybiel (1975), motion sickness represents:

> ...a constellation of delayed epiphenomena (mainly the signs and symptoms of motion sickness--ed.) precipitated by repetitive vestibular sensory inputs that are either abnormal or (if normal) encounter an abnormal integrative pattern. The immediate origin of cardinal symptoms is in nonvestibular systems; hence, first-order responses (at least) must reach cell groups via preferential pathways (presumably in the brain stem reticular formation) not used under natural stimulus conditions.

Certain features of the theory were summarized by Homick (1979):

> The majority of research in progress to define the etiology of space motion sickness is generally based on the premise that the syndrome is the overt manifestation of unresolved sensory conflict. In all likelihood, modifications in otolith behavior which occur during the first few hours in weightlessness are a primary factor in creating sensory conflict. The conflict may be in part intralabyrithine in origin. That is, the normal synergy that is thought to exist between the semicircular canals and otoliths may be disrupted, thus resulting in modified neural outflow. Also, it is probable that intermodality conflict involving the visual, vestibular and the touch, pressure and kinesthetic senses occurs. The net result may be an inability of the central nervous system to properly integrate the mismatched sensory influx. Adaptive processes in the central nervous system presumably occur as evidenced by the gradual and complete recovery from symptoms of motion sickness.

The hypothesis that labyrinthine fluid imbalances may result from the well-documented cephalad shifts of blood and body fluids in zero-G and may cause abnormal vestibular function leading to symptoms typical of motion sickness originated following the Skylab program, and is still viable (Tonndorf, 1982; Wolfe et al., 1981). Some additional support for the concept is based on the knowledge that acute changes of air pressure in the middle ear can induce vertigo (Benson and King, 1979). Another suggestion is that fluid shifts may result in decreased circulating levels of isorenin-angiotensin, leading to direct effects on the chemoreceptor trigger zone (Barrett and Lokhandwala, 1981).

Treisman (1977) postulated that the mechanisms of motion sickness function in the physiologic responses to certain poisons. Sometimes called the evolutionary theory, it suggests that the disequilibrium, malaise, nausea, vomiting, and other manifestations of motion sickness evolved as a pattern of response to such life-threatening situations as the ingestion of foodborne neurotoxins, and that this response registered in survivors as a warning against future exposure to such poisonous substances. Money and Cheung (1982) tested Treisman's hypothesis by injecting labyrinthectomized dogs with four, and later, five emetic poisons. Removal of the vestibular apparatus resulted in marked impairment of the vomiting response to lobeline, levodopa, and nicotine, but not to pilocarpine or apomorphine. They concluded that the vestibular apparatus is part of the normal mechanism for the emetic response to certain poisons and that Treisman's theory had merit.

In formulating their conclusions, Money and Cheung (1982) cited the basic report of Wang and Borison (1952) who developed a general physiologic method for differentiating between emetic substances that are peripherally or centrally active. Wang and Borison (1952) demonstrated the existence of an emetic chemoreceptor trigger zone in the floor of the fourth ventricle, corresponding anatomically to the area postrema. They concluded that the medullary emetic mechanism consisted of two anatomically close but functionally separate parts: first, an emetic center near the fasciculus solitarius and underlying reticular formation, and second, a chemoreceptor trigger zone. Citing a report of Wang and Chinn (1952) which showed that dogs became resistant to swing sickness after ablation of the trigger zone, Wang and Borison (1952) suggested that further validation of this effect might support the concept that vestibular impulses elicited by motion traverse the nodulus and uvula of the cerebellum and the trigger zone, finally reaching the medullary vomiting center. They suggested that such studies could prove valuable in determining the mode of action of anti-motion sickness drugs.

Parker (1980) noted that most investigators of the vestibular system tend to believe that space sickness is the result of sensory mismatch; that is, the disparity between orientation inputs received from different receptors. Currently, many investigators regard the sensory conflict theory as the most viable; however, it remains ill-defined in terms of physiologic mechanisms. Members of the ad hoc Group regarded the sensory conflict theory as a concept that may be useful in planning research and designing neurophysiologic and neuroanatomic experiments, but that it is insufficient, at its present state of development, to explain any underlying mechanisms of space sickness.

In summary, exposure of an unaccustomed subject to certain types of unusual motions is the common cause of motion sickness. Space sickness is thought by many experts to result from exposure to a combination of head and/or body movements and weightlessness, but this has not been fully documented. The mechanisms of motion and space sickness are unknown; hence, current investigations are based mainly on theories involving neural mismatch, sensory conflict, or certain postulated effects of the cephalad shift of blood volume and body fluids that occurs in zero-G.

D. COUNTERMEASURES

In view of the incomplete understanding of the underlying mechanisms and the pathogenesis of motion sickness and its space sickness counterpart, NASA currently has little option for dealing with the problem except to rely on anti-motion sickness drugs and, possibly, to assign to key positions in space crews those who have demonstrated resistance to space sickness on previous missions. Preselection of individuals who are resistant to motion sickness,

and preflight habituation to provocative vestibular stimulation on the theory that this would prevent or ameliorate space sickness or hasten the habituation process appear logical and desirable. For instance, human habituation to provocative vestibular stimulation has been demonstrated in ground-based studies. However, the question whether the tolerance to ground-based or aircraft-based vestibular stimulation will transfer to the spaceflight situation and will influence susceptibility to space sickness has not been answered, although Soviet authorities seem convinced that preflight exposure to vigorous aerobatic maneuvers offers some protection against space sickness.*

Among the approaches that are being investigated in regard to preventing or treating space sickness are prophylactic and therapeutic medications, vestibular adaptation training, preselection of resistant individuals, restriction of head and body movements, and autogenic-feedback (biofeedback) training. However, since research on these several approaches has not yet provided practical methods for spaceflight, NASA has relied mainly on prophylactic and therapeutic use of drugs during actual space missions. The need for expanded research emphasis on alternate approaches is underscored by the observations that prophylactic and therapeutic use of drugs is not, by itself, reliably and completely effective, and carries with it the problem of adverse side-effects.

Anti-motion sickness drug evaluations in ground-based studies and in aircraft have shown that agents possessing central anticholinergic actions and drugs that augment central sympathetic activity are effective against acute motion sickness (Chinn and Smith, 1955). Currently, NASA uses the orally administered combination of scopolamine (0.35 mg) and dextroamphetamine (5.0 mg) for premedication or treatment. During sleep periods, promethazine (Wood, 1982) or diazepam (Olson, 1982) has been suggested. The NASA strategy for anti-motion sickness medication includes preflight evaluation of drug effectiveness against the effects of provocative vestibular stimulation and observation of side-effects. Astronauts scheduled for space missions are treated according to the following plan: (1) premedicate if there has been no previous space flight experience, or if there is a positive history of space sickness; (2) do not premedicate if there is no history of space sickness during previous flights; (3) treat inflight if symptoms occur.*

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* Unpublished date presented during the meeting of the LSRO ad hoc Working Group on Space Motion Sickness, September 13-14, 1982, at FASEB Headquarters, Bethesda, MD.

Wood and Graybiel (1972) reported that scopolamine was the most effective individual drug and scopolamine-amphetamine the most effective drug combination for preventing motion sickness in volunteer subjects during controlled tests in the Pensacola Slow Rotating Room. However, in subsequent tests in the same facility, the combination of promethazine (25 mg) and ephedrine (25 mg) was shown to be superior to all other drugs in that particular provocative environment (Graybiel et al., 1975; Graybiel and Knepton, 1977; Johnson et al., 1976). In addition, these studies contributed further knowledge of the marked biologic individuality of drug responses, reemphasizing the need for individual pretesting for antinauseant efficacy and for side-effects.

A non-pharmacologic countermeasure that holds promise is autogenic feedback training (Cowings and Toscano, 1982; Toscano and Cowings, 1982). This type of method has demonstrated effectiveness in salvaging for flying duties a substantial number of U.S. Air Force aircrew personnel who suffered incapacitating airsickness (Gardner et al., 1983). Whether it may prove to be effective and practical for spacecrew members remains to be demonstrated. NASA's research plans include consideration of this question.

Attempts were made to preadapt some members of the Skylab crew to provocative vestibular stimulation by a regimen of repeated series of head movements with subjects seated in a rotating chair, and by weekly sessions of aerobatics in high performance aircraft (Skylab 4 crew members) (Homick, 1979). Although these procedures appeared to reduce susceptibility to motion sickness induced by ground-based Coriolis accelerations, there was no evidence of their possible benefit during the space flight missions of the Skylab program. Nevertheless, the concept of pre-space flight vestibular habituation using ground-based or airborne methods has not been exhausted.

Soviet space medical investigators have tested several physical devices including pneumatic cuffs on the thighs, lower body negative pressure, and a special headgear. They have reported beneficial results in management of space motion sickness from the use of the headgear, which they call the prophylactic cervical support. It consists of a soft cap attached to the shoulders by adjustable rubber constraints. The device imparts a mechanical load on the cervical spine and the occipital-cervical antigravity muscles, and also tends to limit head movements. It is said to have prevented illusory sensations and to have diminished the symptoms of space sickness (Matsnev and Homick, 1981). It is understood that development and test of the device are continuing in the U.S.S.R., and it is listed as a possible item for test in the U.S. space motion sickness research and technology program (National Aeronautics and Space Administration, 1982).

Thus, NASA currently relies on the prophylactic and therapeutic use of anti-motion sickness drugs, procedures that have proved only partially effective in preventing or controlling the symptoms of space sickness. Identification of resistant individuals, preflight vestibular habituation, transferability and enhancement of habituation, autogenic feedback training, devices to restrict head movement and load the cervical muscles, and alternate types of drugs are being investigated in hopes of finding practical, effective methods of avoiding, preventing, or controlling space sickness.

IV. THE NASA RESEARCH AND ANALYSIS PROGRAM IN SPACE MOTION SICKNESS

Of the eight major problems addressed by NASA's Biomedical Research Program, space sickness currently has the highest priority (Soffen and Bishop, 1982). A program of research and analysis in Space Motion Sickness is included in the Biomedical Research Program of the Life Sciences Division at NASA Headquarters. Responsibility for the scientific management of the two Research and Technology Objectives and Plans in space motion sickness is assigned to the appropriate RTOP's managers at the Johnson Space Center and the Ames Research Center. Together, the two RTOPs managers supervise a total of 24 research tasks of which 19 are by university grants or contracts. In addition, they conduct their own scientific investigations of space sickness in their NASA center laboratories.

Most of the research conducted under the two space motion sickness RTOPs is ground-based; however, through these investigations, hypotheses are developed that must ultimately be tested in space. The program is, therefore, closely related to the planned series of inflight experiments on the Shuttle and Spacelab.

The FY 1983 budget for the biomedical research program in space motion sickness approximates $2.0 million, of which $1.4 million is extramural. Both the extramural and intramural programs undergo periodic revision in response to changes in scientific guidance, changes in priority, the addition of new, peer-reviewed research, and the phase-out of completed or downgraded tasks.

Table 4 lists research recommended by two major life sciences advisory groups (Bricker, 1979; Whedon, 1978), and shows, by task number, the applicable research in the current (FY 83) program under the two primary NASA RTOPs in space sickness. Blanks in the table indicate no research is specifically documented under the two RTOPs at the present time. However, not shown in the table are tasks pertaining to certain operational and flight test aspects of space sickness that are programmed or planned to be carried out under separate RTOPs. It is clear, from comparison of the scope and amount of research and development that have been documented as necessary to resolve the problem of space sickness, that the needs exceed the available FY 83 resources by a wide margin. Moreover, achieving an ideal solution to the problem requires the elaboration of etiologic and mechanistic factors that have eluded several decades of scientific investigation.

Opinions of the members of the LSRO ad hoc Working Group on Space Motion Sickness on the merits of the current NASA ground-based program are based upon abstracted information in the NASA RTOPs and RTRs, on information presented during the meeting of September 13-14 by NASA scientists, and on their own knowledge of

Table 4. Correspondence between advisory group guidance* and NASA's FY 83 research and technology program in space motion sickness

Suggested research and technology	Johnson Space Center RTOP 199-20-21 applicable tasks	Ames Research Center RTOP 199-20-22 applicable tasks
SHORT- AND MID-TERM (<5 y)		
Behavioral responses to otolithic stimulation†:		
Human, ground-based and spaceflight	02	—
Animal, ground-based and spaceflight	—	—
Epidemiology†:		
Analyze astronauts' individual anti-motion sickness training versus space sickness experience	—	—
Improve methods of inflight data collection	programmed in a separate RTOP	—
Countermeasures:		
Identify susceptible and resistant individuals†	02, 09, 16	—
Anti-motion sickness training--		
Vestibular and associated sensory systems		
ground-based	16	—
airborne	—	—
Autogenic feedback	to be programmed under a separate RTOP	10 —
Anti-motion sickness drugs†		
Seek improved drugs and drug combinations	09, 16	11
Test alternate routes of administration	16	—
Improve drug delivery systems	—	—
Methods and facilities†:		
The need for parabolic flight	09	09
Develop acceleration devices for use in Spacelab	programmed in a separate RTOP	programmed in a separate RTOP
Develop methods to facilitate adaptation	16	—

Table 4. (cont.)

Suggested research and technology	Johnson Space Center RTOP 199-20-21 applicable tasks	Ames Research Center RTOP 199-20-22 applicable tasks
LONG-TERM (>5 y)		
Biologic mechanisms:		
Of motion sickness and space motion sickness--		
Test and elaborate current hypotheses--		
Sensory conflict	04, 09	05, 22
Otolith dysfunction	programmed in a separate RTOP	programmed in a separate RTOP
Altered semicircular canal response	17	15,22
Fluid shifts	03	--
Of marked differences in individual susceptibility	--	--
Of adaptation to weightlessness	09	--
Neuroanatomy and physiology of vestibular systems		
Vestibular end organ	05	15, 20, 22
Related spatial sensors	--	--
Locate second order otolithic neurons	--	04, 14, 15, 18
Physiologic organization of otolith pathways within vestibular nuclei	--	04
Characterize response of second order otolithic neurons to motion stimuli	--	14
Characterize interactions of vestibular, visual and other spatial-sensory inputs at level of second order neurons	03, 09, 17	04, 05, 09, 17, 21
Extend studies of vestibular system responses and interactions to further stages of relevant pathways	--	11, 14, 18
Vomiting areas of brainstem		
Further identify and characterize areas in brainstem involved in vomiting	--	03, 11, 21, 23
Effects of inputs from vestibular, visual, and other sensors on vomiting areas of brainstem	--	--
Determine whether stimulation of vestibulo-cerebellum areas causes vomiting	--	03, 05

* From reports of two advisory groups (Bricker, 1979; Whedon, 1978). This table is merely an example, for NASA's scientific advice is derived from multiple sources. The aggregate of NASA RTOPs that include work on space motion sickness is sufficiently comprehensive to embrace all the research suggested in this table.

† Has implications for long-term studies also.

Key to the task numbers in Table 4.

Task No.	Investigator	Location
Johnson Space Center RTOP #199-20-21		
-02	Reschke (mechanisms)	Johnson Space Center
-03	Parker	Miami U., Ohio
-04	Igarashi	Baylor U., Houston
-05	Correia	U. Texas, Galveston
-06	Anderson	U. Michigan, Ann Arbor
-09	Lackner	Brandeis U., Waltham
-14	Oman	MIT, Cambridge
-16	Begioanni (counter-measures)	Johnson Space Center
-17	Black	Portland, Oregon
Ames Research Center RTOP #199-20-22		
-03	Mehler	Ames Research Center
-04	Goldberg	U. Chicago
-05	Daunton	Ames Research Center
-09	Young	MIT, Cambridge
-10	Cowings	Ames Research Center
-11	Brizzee	Tulane University
-14	Wilson	Rockefeller U., New York City
-15	Perachio	U. Texas, Galveston
-17	Bizzi	MIT, Cambridge
-18	Graybiel	MIT, Cambridge
-20	Tomko	U. Pittsburgh
-21	Miller	Rockefeller U., New York City
-22	Correia	U. Texas, Galveston
-23	Crampton	Wright State U., Dayton
-25	Norris	Tulane U., New Orleans

the space sickness problem. Most comments have been favorable in terms of the described experiments and approaches and quality of the investigators doing the work. Some members felt that much of the basic neuroscience in the program is not directly related to motion sickness so as to qualify for NASA support although they had no quarrel with the scientific excellence of the particular studies. This was a debatable subject on which a majority of the Working Group were convinced that much basic neuroscience must be accomplished before the etiology and mechanisms of motion sickness and space sickness can begin to be reasonably understood. Consequently, the majority view was that NASA's current program of ground-based research and development serves its objectives and approaches, is appropriate with respect to current studies, but insufficient in level of effort. It is understood that opportunities for increasing the level of effort of the program now exist within NASA, and the Working Group endorses a careful expansion of the program along lines suggested in Sections V and VI of this report.

During the deliberations of the LSRO ad hoc Working Group, problems of space sickness associated with the Shuttle flights received considerable publicity. NASA officials recognized the necessity to expedite and broaden the scope of research aimed at understanding and controlling the disorder. In this regard, NASA conducted a workshop at the Johnson Space Center in June, 1982, convening a group of 33 individuals including responsible NASA research managers, staff scientists, and a number of prominent investigators who are involved in studies of space and motion sickness. A report of the proceedings has been published (Homick, 1982).

A majority of the studies and their priorities recommended by the workshop subgroup on physiology are consistent with the opinions of the LSRO Working Group. The biological systems approach identified in the Proceedings (Homick, 1982) would offer a particularly promising methodology for research planning and experimental design. Similarly, the broadening of the disciplinary approach, the emphasis on chemical-mediating mechanisms in the stimulus-to-vomiting sequence, and the use of interdisciplinary teams to define the physiological correlates of the conflict and mismatch theories and the specific linkages to the effector mechanisms of space sickness are examples of research strategies supported by the LSRO ad hoc Working Group on Space Motion Sickness.

V. OBSERVATIONS OF THE AD HOC WORKING GROUP ON SPACE MOTION SICKNESS

For convenience of presenting the views of the Working Group, this section is divided into five topics: (1) cause and mechanisms, (2) peripheral sensory organs, (3) central nervous system structures, (4) methodology, and (5) countermeasures and other aspects. The suggested research and development are intended to assist NASA program managers in formulating plans for future research and technology in space sickness; however, they are also intended to serve as examples of opportunities for interested scientists to participate in NASA-supported scientific endeavors.

A. CAUSE AND MECHANISMS

1. Assessment

Many authorities seem satisfied that the cause of motion sickness and its space counterpart is unusual acceleration of the vestibular end organs. Although manned space flight experience strongly suggests that movements of the head are necessary to induce space sickness (see p.11), this has not been adequately documented, and a fundamental question persists: "What is the stimulus for space sickness?" Some members of the Working Group consider the stimulus multimodal including head and body movements which are seemingly unusual because of a lack of motor programming to deal with weightlessness, inappropriate central interpretation of mixed sensory inputs caused by weightlessness, and possible psychic influences. The precise targets for sensing the provocative stimuli during space flight have not been definitely established; for example, are the otolith organs or the semicircular canals, or both, involved?

The specific physiologic mechanisms of motion and space sickness remain obscure. Likewise, the broader biologic significance of motion sickness is not understood although the concept of Treisman (1977) offers a possible evolutionary perspective (see p.13). The Working Group discussed prevailing theories of mechanisms (see p.12), but considered that none adequately explains the genesis of the syndrome.

With regard to where the emphasis should be placed on investigative approaches to elaborating the etiology and pathogenesis of space sickness, the comments of Chinn and Smith (1955) are still germane:

> In the onset of motion sickness, it is apparent that the central and autonomic nervous systems are repetitively bombarded with impulses along afferent pathways not only from the vestibular

> organ, but, also, from other sources such as the optic, proprioceptive, and visceral systems. The importance of these latter stimuli are not minimized, but since motion sickness can be prevented by interruption of vestibular impulses (bilateral labyrinthectomy, sectioning of 8th nerve) this pathway deserves primary emphasis.

Further, Benson's summary statement in 1977 quoted in Bricker (1979), may still offer the best general guidance:

> The features of the sensory and autonomic disturbances that have come to be called space sickness are thus very similar to those produced by motion stimuli in a terrestrial environment. Although similarity does not prove that the causal mechanisms of space sickness are necessarily the same as those of motion sickness, in the absence of evidence to the contrary, parsimony dictates that space sickness must be considered just another form of motion sickness.

General observations of the Working Group on the state-of-the-art in motion and space sickness highlight the immensity and complexity of the problem of elucidating the underlying mechanisms. A consideration that is related to the question of the etiology of space sickness is whether the vestibular organs do, if fact, remain physiologically normal during space flight. There is a paucity of reported research on the biochemistry of motion sickness. Little is known about the neuropharmacology of synaptic mechanisms of the sensory end organs, afferent pathways, and at the central processing and effector sites. It is not known whether the "final" stimuli in the reflex arcs of nausea and vomiting are neurogenic or chemogenic, nor are the essential neural connections involved in motion sickness fully identified.

It is known that a diversity of afferents comes from the labyrinth, but little is known of how they are distributed to the secondary neurons which also receive input from other sensory systems or neural structures. This impedes understanding of relationships between labyrinthine responses and central processing. For example, how valid is the assumption that an isomorphic causal relationship exists between vestibular afferent impulses from a standard head movement and the observed neural responses in identified, anatomically-linked secondary neurons? Moreover, how does concomitant input from other sensory systems modify the fidelity of neural transmission of afferent input by vestibular nuclei neurons? The roles of the diencephalon and the cerebral cortex in the etiology

of and habituation to motion sickness are essentially unknown (p.32 et seq.). For instance, the anatomic and physiologic properties of the vestibulothalamic and vestibulocortical pathways are not clearly understood (see review, Correia and Guedry, 1978).

Answers are needed to such basic questions as, for example: where and how processing of normal motion-induced sensory inputs takes place; where and by what means adaptation and habituation to ordinary as well as extraordinary stimuli occur; what parts of the reflex arcs or other neural structures involved in motion sickness demonstrate plasticity in response to motion stimuli; and, at the molecular level, how mechanical energy of deflection of hair cell cilia is converted to electrical energy; how hyperpolarizing and depolarizing receptor potentials are generated; and how the resting level of spontaneous discharge that appears to occur on primary afferent neurons is generated. Finally, it was noted that few reports of interest to space sickness have come from experiments in which some of the newer methods of neuroscience have been employed (p.35, 37). Descriptions of such methods are presented in the 1978-1982 short course syllabi on methodology published by the Society for Neuroscience.*

It is clear that research opportunities abound for innovative investigators who, it is hoped, may expand their interests to include the problem of space and motion sickness.

2. Research suggestions

The inflight patterns of head and body movements of astronauts should be recorded to permit objective comparison between those who do and do not become space sick. This type of analysis should aid in defining the cause of space sickness. In addition, if data are available, analysis of the detailed inflight histories of all past participating astronauts may help to define differences between susceptible and resistant individuals, times of onset of symptoms in relation to mission profiles, and possible contributing events and circumstances.

Experimental technics should be developed and tested in ground-based studies involving both animal and human subjects, in preparation for space flight experiments to determine: (a) whether space flight results in modification of the vestibular sensory neuroepithelium or associated structures (Vinnikov et al., 1979); (b) whether animals with severed vestibular nerves become space sick; (c) whether animals whose neck movements are artifically restricted become space sick; and (d) whether space-flown

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* 9650 Rockville Pike, Bethesda, MD 20814.

animals show any swelling of the sensory epithelium. Future extensions of space flight studies should include observations of other sensory systems that are thought to be involved in the genesis of, and habituation to, space sickness. Flight experiments will require preliminary ground-based efforts to develop and test flight-compatible technics and equipment.

B. PERIPHERAL SENSORY ORGANS IMPLICATED IN MOTION AND SPACE SICKNESS

1. Assessment

Among the sensory systems that may be involved in the initiation of space sickness, the vestibular system stands out as the most likely candidate. Knowledge of the structural and ultrastructural anatomic relationships and mechanical interactions among the otoconiae, cupulae, and the hair cells is incomplete (Dohlman 1971, 1980; Lindeman, 1969). The neurotransmitters and chemoreceptors within the peripheral vestibular neuroepithelium have not been adequately identified (Flock and Lam, 1974). For instance, in mammals, the transmitters at the hair cell synapses and at the first neuronal synapses in the vestibular pathway are not specified. It is likely, however, that the transmitters in question are identical to those that are being studied in the auditory system. (For a review see Guth and Melamed, 1982).

A fundamental need in understanding vestibular function concerns whether the semicircular canals are sensitive to gravity (Estes et al., 1975; Goldberg and Fernandez, 1975); that is, are the canals responsive to linear force under every day conditions on Earth and does this relate to the generation of space and motion sickness? A related question is whether there is any information processing via collateralizing axons between various components of the semicircular canals and the otolith organs (Caston, 1970; Caston and Gribenski, 1982).

Knowledge of the origins and effects of efferent stimuli on the vestibular end organs is conflicting (Goldberg and Fernandez, 1980; Klinke and Galley, 1974), but efferent influences may be significant in the induction of motion sickness and in habituation. What are the mechanisms by which efferent vestibular traffic affects afferent vestibular activity? Does efferent input affect neurotransmitter synthesis in the peripheral vestibular system? What are other trophic effects, if any, of efferent vestibular activity? For example, are the spontaneous activity and dynamic response characteristics of primary afferents affected by prolonged periods of weightlessness?

Information is insufficient for a clear understanding of several aspects of labyrinthine physiology such as development and maintenance of the end organs including biochemical control of otoconial formation, development of accessory structures including the cupula and otoconial membrane, and the control of endolymph production. What is the significance, if any, of the negative calcium balance associated with long space flights on otolith organ and vestibular hair cell function? What regulates calcium turnover in the otoconia? What is the role of Ca^{++} in vestibular hair cell receptor potentials?

The vascular supply of the labyrinth, its neural control, and its effects on labyrinthine function and ionic composition of the perilymph and endolymph have not been fully investigated (Dohlman and Radomsky, 1968). Such studies may be useful in further exploration of the fluid shift hypothesis of motion sickness. Another problem concerns whether interactions and information processing occur among the vestibular end organs under the influence of multi-directional motion stimuli such as, for example, cross-coupled angular accelerations and concomitantly acting linear and angular acceleration. If such interactions occur, are they reflected in the primary afferent output?

A possible site of neural adaptation in the vestibular sensory neuroepithelium in frogs has been proposed (Taglietti et al., 1977), but the neurophysiology, neuropharmacology, and biophysics of the adaptive mechanisms have not been explored.

Many scientists believe the vestibular end organs remain normal during space flight; however, there is some conflicting evidence (Vinnikov et al., 1979). This issue has not been scientifically resolved. It is an important question deserving of high priority in future space flight experiments. Finally, the effects of aging on the integrity of the vestibular organs and their neural supply (Bergstrom, 1973a,b,c) and on susceptibility to motion sickness have not been adequately analyzed despite the existence of a reasonable literature on aspects of this subject. This is of obvious interest to career astronauts.

2. Research suggestions

The afferent input from the vestibular organs resulting from linear acceleration, angular acceleration, and complex stimuli such as cross-coupled accelerations should be identified and characterized at the single unit level. It may be feasible to study the effects of zero-G on the functional and structural integrity of the vestibular end organs by means of repeated parabolic flights. For example, experimental animals exposed to an intensive series of multiple parabolas daily for 3-6 days might offer a method of demonstrating possible structural changes in the labyrinth. With respect to opportunities for space

flight experiments, ground-based research and development are needed to develop technics and equipment for measurement of vestibular nerve activity. In addition, protocols should be developed for precise acquisition and chemical fixation for histopathologic examination of temporal bones of space-flown animals. Ideally, some animals should be sacrificed and tissues fixed at intervals throughout the flight; others postflight. A suitable method of tissue fixation is by intracardiac perfusion plus local perfusion of the inner ear.

The question of whether the semicircular canals are gravity-sensitive should be studied in a normal, alert, chronic preparation in a one-G environment; for example, a monkey with chronically implanted electrodes (Keller, 1976; Louie and Kimm, 1976). Methods should be developed for investigating the interactions between the receptors for linear and angular acceleration as a step toward understanding the stimuli that are imposed by ordinary and by unusual head and body movements in both one-G and zero-G environments.

Stimulation of vestibular system efferents should be investigated in relation to effects on afferent activity in alert primates in physiologic situations in which the efferent system may participate. Qualitative and quantitative changes, if any, in neurotransmitter activity at various levels in the vestibular system that result from efferent inputs should be determined.

Identification of the neurotransmitters in the afferent pathways, particularly at the end organ, could lead to practical pharmacologic studies of candidate anti-motion sickness drugs, and possibly, of anti-vertigo drugs. In addition, further studies should be done on the possible existence in the vestibular nerve of postganglionic autonomic nerve fibers (Densert, 1975; Ross, 1981; Ylikoski et al., 1979). If this is confirmed, the role of such a pathway on end organ function should be investigated.

A promising approach to continue the investigation of the fluid shift hypothesis of space sickness would be to determine changes in auditory threshold during cephalad shifts of blood volume. If confirmed, such changes might suggest concurrent changes in vestibular end organ sensitivity or function. Human and animal subjects exposed to head-down tilt and animals exposed to foot-to-head acceleration might be appropriate models for such studies. In addition, inflight test of spacecrew members' hearing may be a feasible extension of such studies.

Another basic study having significant implications for the fluid shift hypothesis would be to demonstrate a meniere's type response (Wolfe et al., 1981) to frequency analysis testing of the vestibuloocular system in an astronaut during an episode of space sickness or following recovery.

C. CENTRAL NERVOUS SYSTEM STRUCTURES IMPLICATED IN MOTION AND SPACE SICKNESS

1. Assessment

Pathways through the central nervous system resulting from motion stimuli have been only partially delineated. For instance, the pathways through the cerebellar nuclei are unknown. In fact, the anatomic mapping of pathways and centers of response to gravito-inertial stimulus inputs from the involved sensory systems is only fragmentary. However, the neuroanatomy associated with motion sickness appears to be advanced relative to what is known of the functional significance of the defined pathways and connections involved.

A fundamental question that indicates a need for substantial additional research concerns where and how the central nervous system processes motion-induced signals from the vestibular, visual, proprioceptive, and somatosensory receptors. It is thought that the vestibular nuclei and parts of the vestibular cerebellum have prominent roles in such information processing, but detailed data on this are lacking. Examples of other structures of the brain stem that have been implicated in the pathways of response to motion-induced inputs and that may have a role in processing include the nucleus prepositus, nucleus intercalatus, and the nucleus of Roller. These all seem to have direct or indirect connections with the vestibular nuclei and the nucleus tractus solitarius as well as area postrema. Connections between the solitary nucleus and the reticular formation in the region of the vomiting center have also been identified. In addition, neurons have been identified in which the cell body is located in the area subpostrema inside the blood-brain-barrier, but outside the area postrema. The dendrites from some such neurons extend through the blood-brain-barrier into area postrema, and axons of such neurons extend into the nucleus of the solitary tract. It appears possible that some such neurons may serve to monitor electrical events or even the chemical milieu in the area postrema outside the blood-brain-barrier and to transmit appropriate signals to the non-gustatory part of the nucleus of the tractus solitarius which may be involved in mediating the vomiting reflex to different types of stimuli, including various modalities of motion. Thus, numerous connections have been found that are of interest in relation to motion sickness although very little is known about their functions (Cottle and Calaresu, 1975; Hosoya and Matsushita, 1981; Morest, 1960, 1967; Vigier and Portalier, 1979; Vigier and Rouviere, 1979). Moreover, there are, at present, no adequate models or methods of analysis for resolution of the questions on central processing.

Another problem, of equal importance to information processing, is the matter of habituation and adaptation to motion-induced stimuli. The process of adaptation at the cellular level in the vestibular nuclei, if it occurs there, or the vestibular neuroepithelium, is essentially unknown. Similarly, the cerebellum is thought to have a prominent role in habituation, but where and how it takes place are not clear. Is the plasticity in the cerebellum or is the cerebellum merely a part of a motor loop for other areas of the brain that may be involved in habituation? What are the effects of ablation of parts of the cerebellum on habituation? Are neurons that project to the cerebellum, thence into the brain stem, inactivated by cerebellar lesions?

Some preliminary evidence suggests that an endogenous "vomiting substance" may be an essential part of the emetic reflex arc in motion sickness (for instance, see Daunton, 1982). An interesting question in this regard is a possible role of the spongiform bodies of the circumventricular organ system in the brain ventricles (Kelly, 1982); however, there are no reports that these organs are secretory. The possible existence of an endogenous vomiting substance is of interest for several reasons including the uncertainty about whether the final afferent link in the emetic reflex arc is neuronal or chemical (Borison and McCarthy, 1983).

Receptors of the antimuscarinic and antihistaminic types have been found in the vestibular nuclei (Palacios et al., 1981; Wamsley et al., 1981); however, available information on the biochemistry of the receptors and neurotransmitters in the vestibular nuclei, as in other parts of the vestibular system, is very limited. What other types of receptors and transmitters may be found in the reflex arcs associated with motion and space sickness?

The effects of the brain stem reticular system on responses to motion stimuli at the level of the vestibular nuclei are not clearly defined and have not been carefully studied in recent years. Is the efferent process that is associated with motion sickness augmented by proprioception, vision, or stress? Available information on the functions of the diencephalon and cerebral cortex in mediating motion sickness and habituation is meager. Motion-induced reticulocortical input followed by inhibitory corticothalamic outflow might influence responses to the stimuli that cause motion and space sickness. However, decerebration does not prevent motion sickness or the emetic response in some species (Money, 1970; Tyler and Bard, 1949). Novel stimuli can generate anxiety and concomitant sympathetic activation in species having higher cortical integration, but a majority of experts believe that anxiety probably does not influence susceptibility to, or promote, motion sickness. Nevertheless, some evidence points toward anxiety as a contributing factor in airsickness (Tucker and Reinhardt, 1966), and the powerful influence of

the cerebrum over brain stem and cerebellar mechanisms (Money, 1970; Penfield and Erickson, 1941; Reason and Brand, 1975; Robinson and Mishkin, 1968) suggests that higher cortical activity is capable of exerting both suppressive and facilitatory influences on motion and space sickness neural processes. Questions remain as to exact neurophysiologic mechanisms and the extent of such effects. A question also arises as to whether behavioral intervention technics (see p.16) might be operative via a cortico-thalmic-reticular, corticodiencephalic, or other mechanism and whether such behavioral-cognitive training technics could be effective as countermeasures to space sickness and to what degree.

Other problems that need investigation concern the possible role of the deep cerebellar nuclei in producing motion sickness. Neurons in these nuclei respond to motion stimuli, and the deep nuclei have some functions related to postural responses and the storage of balance information. For example, lesions of the cerebellum are associated with certain long-lasting effects on eye movement control such as periodic, alternating nystagmus, and there is interest in whether the deep cerebellar nuclei are involved in the habituation process, especially to inputs that occur over long time periods. Although a great deal is known about the function of the flocculus, relatively little is known of other areas of the cerebellar cortex, such as nodulus and uvula, that have prominent projections into the deep cerebellar nuclei. Interest also concerns the possible roles of the inferior olive and inputs via the climbing fibers and mossy fibers in motion sickness and habituation. Related to these matters is the question of how visual fixation is achieved and maintained in moving visual surrounds or with movements of the observer. Finally, a question persists as to whether "conflict" neurons exist, and, if so, where?

2. Research suggestions

Because of the large amount of essential biologic data that must be acquired to provide the basis for a practical understanding of motion and space sickness, the Working Group suggests that a long-term, broad-based program of basic research is needed to unravel the complexly interconnected neural circuits and to elucidate the intricate biologic mechanisms involved. Examples follow of the types of investigations that are considered advisable.

Identification of neuronal circuits in the vestibular nuclei and the vestibular centers of the cerebellum, their connections to the emetic control mechanism, and their roles in motion sickness needs greater emphasis. Where practical, natural stimuli should be used in studies of sensory interactions to trace the projections of afferent neurons of the spatial end organ receptors to the vestibular nuclei and their connections with second order neurons. Identified pathways converging back on secondary neurons should be included with such studies.

A plan should be developed for (1) neuronal mapping of areas of the brain that are considered to be primarily responsive to motion sickness stimuli; (2) identification and characterization of the neurotransmitters, neuromodulators, and receptors in the mapped pathways and connections; and (3) determination of the function of the identified pathways and connections and their role in the habituation to motion and space sickness.

An important approach to the improvement of medicinal management of space sickness and to aid in the discovery of more effective drugs is determining sites of drug action. For instance, Wamsley et al. (1981) demonstrated high densities of muscarinic receptors in the medial vestibular nuclei in the rat. They used radiolabeled quinuclidinyl benzilate ([^{3}H]QNB) and autoradiograpy of selected sections of the brain stem in these light microscopic studies. A similar study from the same laboratory identified large concentrations of histamine-H_1 receptors in the medial vestibular nuclei (Palacios et al., 1981). These studies are of considerable interest because such drugs as scopolamine, an anticholinergic, and dimenhydrinate, an antihistaminic, may mediate their anti-motion sickness effect via the identified receptors in the medial vestibular nuclei. Also, different kinds of muscarinic receptors have been identified. Precise pharmacologic definition of the types of receptors in the vestibular nuclei could suggest new anti-motion sickness drugs.

Thus, identification of neurotransmitters and neuroreceptors in relevant areas of the brain could lead to a new pharmacologic approach to space sickness. More effective drugs, with fewer side-effects, seem highly desirable and may already exist in untested inventories of drug companies.

Other studies are needed to determine whether the link from the vestibulocerebellar axis into the emetic reflex arc in motion sickness is neuronal, chemical, or both.

Hypotheses should be formulated on which to base experiments to examine the interactions among vestibular, visual, proprioceptive, and somatosensory inputs resulting from motion exposures associated with terrestrial and space motion sickness. Other experiments should be devised to provide neuronal activity recordings from selected cerebellar sites during the process of habituation to motion stimuli. For example, unit recordings in the uvula and nodulus during motions that are known to cause sickness might prove worthwhile. Also, the input and output activities of the regions of the uvula, nodulus, and flocculus should be determined in response to motion stimuli and related, if possible, to activity in the vestibular nuclei. In addition, the feasibility of determining susceptibility to motion sickness of human subjects having congenital cerebellar cortical degeneration should be explored.

With respect to the sensory conflict hypothesis, studies are needed on the interactions of visual signals with the cerebellum and the vestibular nuclei as an approach to understanding the processing of conflicting sensory information. For example, the relationship between visual suppression in a moving environment and neuronal responses in the vestibular nuclei should be examined. Aspects to be studied might include (1) eye position mechanisms for stabilizing images; (2) neural pathways related to ocular pursuit; and (3) associated long-term storage mechanisms that enhance the low-frequency characteristics of the vestibuloocular reflex. A related question concerns how the velocity signal induced by head movements is formed and how such long-lasting processes are integrated within the nervous system. Finally, experiments are needed to identify relationships and mechanisms between levels of alertness and responses to motion stimuli at the level of the vestibular nuclei.

D. METHODOLOGY

1. Assessment

The Working Group took note of the availability of an array of research methods in neuroanatomy, neurophysiology, and neurochemistry that have evolved in recent years, such as those described by Brizzee and Dunlap (1982; 1983) and in the 1978-1982 short course syllabi of the Society for Neuroscience*. Few reports of interest to the problems of space sickness have appeared in which the newer technics and methods were employed. Examples of some neuroanatomical methods are: the 2-deoxyglucose technic (Sokoloff et al., 1977); immunocytochemical technics (Jones and Hartman, 1978); horseradish peroxidase double labeling (Rustioni, 1978); and electron microscopic autoradiographic methods (Hendrickson, 1978). For neurophysiologic investigations, an emerging technic has been termed "neurokinesiology," a method for investigating correlations between behavioral observations and recorded neural activity in a chronic preparation (Loeb, 1979). Extracellular single-unit recording permits studies of the responses of central neurons to sensory stimuli in alert, moving animals (Humphrey, 1979). One useful noninvasive method for assessing intracranial events such as changes in blood flow and neural activity is positron emission tomographic scanning (PET scanning) (Phelps et al., 1982). (Other examples are noted on p.37).

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As a general principle, research and development on methods should be emphasized when they show promise of aiding the advance of research in basic problems of motion sickness, in particular the elucidation of underlying mechanisms.

The problem of finding the most appropriate animal model, or models, was discussed, with emphasis on the need to continue a search for suitable animal models that offer advantages not only in physiologic response, but also of availability, cost, and ease of handling. Thus far, animals that most closely match humans in terms of responses to motion and anti-motion sickness drugs are cats, dogs, and squirrel monkeys. Animal models such as rats and other species that do not vomit, do however, exhibit certain visceral signs of sickness such as salivation. Whether such thoroughly studied and relatively inexpensive species have a good potential in studies of motion and space sickness needs further consideration.

Functional tests of the vestibular apparatus fall short of ideal; for instance, there is currently no dynamic test for otolith function in humans. There is no clear test of the vertical semicircular canals. Counter-rolling, a static test of otolith function, is less than optimal. A need exists for a set of functional tests for assessment of all the "spatial" receptor organs and their interactions. The possibility of a vestibular brain stem evoked potential (Aran et al., 1980; Elidan et al., 1982) is appealing.

A recurring question is the utility of parabolic flight in aircraft for studying space sickness. While this method is the only one short of space flight that can produce more than momentary weightlessness, its practical utility for resolving problems of space sickness should be reconfirmed if possible.

Finally, a question arose concerning possible utility of the clinostat as a means of simulating some aspects of zero-G for studies of vestibular responses (for review, see Gordon and Shen-Miller, 1971). Members of the Working Group did not consider that the clinostat offers a valid method of simulating weightlessness for investigations of space sickness. However, devices for tilting experimental subjects in pitch and roll have proved valuable in characterizing physiologic responses of the otolith organs (for example, Fernandez and Goldberg, 1972; 1976).

2. Research suggestions

The neurochemistry of selected anatomic sites in the putative nauseogenic and emetic reflex arcs of motion sickness should be studied to identify and characterize all chemoreceptors and neurotransmitters involved. Methods are needed for determining whether neurotransmitters that are functionally specific in the

emetic and nauseogenic reflex arcs are released at the defined sites and the time course and nature of the release. The preliminary work on the existence of a vomiting substance (Daunton, 1982) should be extended to confirm its existence and to charactize it. Therapeutic counteraction or inactivation may then be feasible.

For determining the sensitivities to inhibitory or blocking agents of active sites in the emetic reflex arc of motion sickness, a promising method is by injection of drugs via implanted cannulas before, during, and after exposure of the test animal to sickness-inducing motion stimuli. Theoretically, neurochemicals with apparent selectivity for motion sickness in implicated pathways would be targets for pharmacologic intervention.

Some of the newer technics that show promise for helping to identify and characterize receptor sites in the nervous system include the radioreceptor assay (Enna, 1980); in vivo receptor binding of radiolabeled drugs combined with light microscopic autoradiography (Palacios et al., 1981); in vitro autoradiography (Young and Kuhar, 1979); and combinations of such technics with other methods such as fluorescence histochemistry (Roth et al., 1974) or immunocytochemistry (Jones and Hartman, 1978).

Resolution of the autoradiographic and other methods used to locate receptor binding sites in the nervous system is inadequate for precise localization. For instance, electron microscopic autoradiographic processes have a limit of resolution of approximately 1500 Ångstrom units, which is larger than a synapse (Murrin, 1980). Promising electron microscopic technics include use of peroxidase labeled ligands or antibodies to purified receptors (Vogel et al., 1979).

Sequential double-labeling technics have been helpful in identifying and studying sites in the brain stem that take up glucose differentially while the test subject is exposed to motion stimuli. (For example, see: Agranoff et al., 1980; Altenau and Agranoff, 1978; Brizzee and Dunlap, 1982, 1983). These and other methods should be refined to enable identification of neural pathways that mediate motion sickness stimuli and may be involved in habituation.

Efforts should be extended to develop alternate methods of testing otolith organ function and a spectrum of tests to assess all the receptor organs and their interactions. Such a group of tests should aid in identifying individuals who are susceptible as well as those who are resistant to motion sickness. It may be feasible to develop procedures for measuring brain stem vestibular evoked potentials (Aran et al., 1980; Elidan et al., 1982). It would seem useful to explore neural correlates of sensory conflict by measuring the difference between eye movements and patterns of firing rates under certain conditions in which there is a mismatch between visual and vestibular stimuli.

The search for the most suitable animal models for studies of terrestrial and space motion sickness should be continued. Objective methods of determining the occurrence of motion sickness in experimental animals, in addition to vomiting, should be applied to animals in which the vomiting response is absent or unreliable. Further investigation of the vegetative responses of rodents, birds, and amphibia to motion stimuli may be advisable to determine whether these species demonstrate a measurable end point that could make them useful for motion sickness studies and for screening anti-motion sickness drugs (Coil et al., 1978; Hulse et al., 1977; Mitchell et al., 1977a,b; Ossenkopp, 1982). In addition, genetic mutants (pallid mice) exist that lack otoconia, and may offer a useful model for studying chronic otoconial deficiency (Lim and Erway, 1974).

A useful method for the in vitro study of various neuronal factors including the effects of drugs and hormones is the electrophysiological slice technic (Prince and Wang, 1981; Skrede and Westgaard, 1971).

With regard to the fluid shift hypothesis of space sickness, the question of possible circulatory influences on the composition of the endolymph and its role in the micromechanics of transduction should be investigated. Methods are needed to simulate postulated changes in intracranial blood pressures and flows (Soffen and Gazenko, 1981) associated with zero-G. Centrifuges offer a means of increasing or decreasing intracranial blood pressure, as may pressor agents, vasodilators, and diuretics. Neural elements controlling vessels supplying the labyrinth should be identified and studied. In addition, studies should be done on the effects of altered blood supply on the ionic and nutritive milieu of such intralabyrinthine structures as the apical tips of hair cells, stereocilia, kinocilia, and cupula and otonial membrane. However, this may be a difficult area of study for which currently available methods may be inadequate.

Whenever feasible, opportunities should be provided for behavioral scientists involved in studies of motion sickness, such as those engaged in autogenic (biofeedback) training methods, to interact with neuroscientists and other scientists in basic and applied aspects of motion sickness research. Joint participation in research planning, workshops, symposia, and collaborative effort in actual research projects should be encouraged.

A new method of measuring motion perception in space is through the use of the illusion of movement when targets are illuminated by flashing lights (Sigma movement). (For an example, see Adler et al., 1981). This technic is useful for demonstrating the presence of internal feedback mechanisms that signal and sustain the illusion of target movement.

Finally, as a guiding principle to improve the fidelity of physiologic responses in motion sickness studies, the ad hoc Working Group suggests that experimental stimuli should be within physiologic limits when possible and tests should be conducted humanely in unanesthetized, alert animals.

E. COUNTERMEASURES AND OTHER ASPECTS

1. Assessment

The ad hoc Working Group is aware of the vigorous planning efforts accomplished by NASA to produce an accelerated program of research and analysis in space motion sickness, and that the development and test of countermeasures are understandably being accorded a high priority. Because the Working Group was requested to consider the problem mainly from the viewpoint of basic research, only a few aspects of countermeasures were discussed. It is assumed that such logical-appearing measures as developing means of identification of susceptible and tolerant individuals, means of preflight habituation, means of self-control of symptoms of motion sickness, inflight enhancement of habituation, and improved drug intervention will continue to receive strong NASA support. It is possible that better anti-motion sickness drugs may already exist in the untested inventories of some drug companies.

On the other hand, it seems generally agreed that the knowledge of the underlying mechanisms of motion and space sickness that should ultimately come from the basic research program is fundamental to the development of the most effective means of preventing or controlling space sickness.

A key question on drug intervention is where and by what practical clinical means can neuronal circuits that have been shown to be essential to the generation of motion sickness be inhibited or blocked. Although progress has been made in locating in the brain stem, receptor sites for certain anti-motion sickness drugs, the actual site of action of scopolamine, for example, is unknown. Some of the newer technics of neuroscience offer opportunities for significant progress in this area.

A question arose during the ad hoc meeting about the reliability of the Shuttle Orbiter environmental control system for keeping the cabin air within acceptable limits for possible toxic contaminants, certain of which have the ability to induce nausea and vomiting. It is understood that, at present, samples of the cabin air are collected periodically inflight for postflight analysis; further, that NASA expects to have the capability for automatic, real time monitoring of cabin air in future missions of the Shuttle Orbiter. No evidence of any problem with the breathing atmosphere of the Shuttle Orbiter came to the attention of the Working Group.

Discussion of the experiments of Bard et al. (1947) and Tyler and Bard (1949) on the prevention of swing sickness in dogs whose noduli and uvuli had been ablated raised the question of whether the interruption of these cerebellar connections as an experimental technic of preventing swing sickness was generalizable to other types of motion stimuli known to induce motion sickness.

The methods NASA uses to report the effects of space flight on the astronauts and the results of inflight experiments were discussed. It was concluded that improvements are needed to assure wider dissemination of such data on a more timely schedule. An important part of management of the program is informing the scientific community about NASA's research needs in order to stimulate sufficient interest to generate proposals from highly competent scientists. One means of doing this is to publish in a scientific journal widely read by biomedical scientists, an account of the important unknown or poorly understood aspects of space sickness and suggested research approaches to gain the desired knowledge.

2. Research suggestions

Until enough is known about specific sites in reflex arcs to permit more precise pharmacologic intervention, development and test of candidate anti-motion sickness drugs should be continued in an effort to formulate and characterize more effective drugs with fewer side-effects. With regard to delivery systems, special notice should be taken by NASA scientists and operational flight surgeons of the occasional report of prolonged mydriasis in patients using transdermal scopolamine (Carlston, 1982; Chiaramonte, 1982; Lepore, 1982; McCrary and Webb, 1982; Roper and Hale, 1982).

Consideration should be given to repeating the experiments of Tyler and Bard (1949) on prevention of swing sickness in dogs by ablation of the uvula and nodulus. If possible, the experimental protocol should be refined in order to help define more accurately the pathways involved in mediating motion sickness. In addition, other types of motion stimuli should be used in such experiments to determine whether the effect of ablation of these cerebellar connections is generalizable to different sickness-inducing motions. Useful data on the function of the nodulus and uvula in motion sickness might be derived from electric or chemical stimulation of these parts of the cerebellum.

Repeated parabolic flights scheduled for the days immediately preceding a spaceflight may facilitate habituation to stimuli associated with zero-G, and such exposures should offer an approach to prediction of individiual responses to weightlessness.

The results of analyses of the cabin air samples of the Shuttle Orbiter might be reexamined to confirm the absence of any toxic contaminant, such as trichloroacetylene, that could be responsible for signs or symptoms associated with space sickness. With

regard to a need for improving the dissemination of information on the effects of space flight on the astronanuts and on the results of inflight experiments, NASA should review its current procedures and consider the feasibility and desirability of increasing the publication of biomedical papers in widely read scientific journals. Brief technical notes that could be published with minimal delay as well as more complete reports in customary scientific format would improve the process of informing the scientific community, which, in turn, should stimulate wider interest in NASA's biomedical problems.

Available data on the effects of aging on the integrity of the vestibular system and on motion sickness susceptibility and ability to habituate should be examined to determine possible needs for additional studies.

In view of the potential scope and size of a comprehensive research program of neuronal mapping, functional determination of pathways, and identification and characterization of neurotransmitters, neuromodulators, and receptors, available hypotheses and models should be refined if possible and new hypotheses developed in order to focus needed research into manageable packages. The implied dimensions of such a comprehensive effort suggest that a collaborative effort by a number of cooperating laboratories would be advantageous.

VI. PRIORITIES FOR RESEARCH AND ANALYSIS

The main objective of the NASA ground-based research and analysis program is to determine the cause(s) and underlying biologic mechanisms of space sickness. This objective includes improvement of investigative technics, methods, equipment, and facilities, and development of effective prophylactic and therapeutic countermeasures. The ad hoc Working Group on Space Motion Sickness was concerned primarily with basic research and associated methodology. The high priority accorded the development and test of improved countermeasures to deal with the problem, such as improved means of pharmacologic intervention, is understood as being operationally essential for NASA. However, the primary basis for progress in prevention and treatment is knowledge of the true etiology and underlying mechanisms of the disorder, achievement of which requires a sustained, broad-based research program. NASA's current and planned research in this field, augmented by the suggestions of the ad hoc Working Group, should ultimately provide the knowledge needed for solution of the problem.

As a general approach, a program should be planned to map areas of the brain thought to be involved in space and motion sickness and to identify and characterize the associated chemoreceptors, neurotransmitters, and neuromodulators. Related studies should probe the roles of the identified pathways and regulatory substances in the mediation of, and habituation to, space and motion sickness and as leads for discovering new drugs.

The ad hoc Working Group recommends the order of priority shown in Table 5 as appropriate for the suggested research and development in this problem area. The suggestions in the category, "Stimulus-Response Relationships," are considered most important; those in the second group, "Reflex Pathways," should be next in priority, followed by those in "Related Vestibular Neurophysiology." However, if future studies confirm the essentiality of the vestibular apparatus in the mediation of space sickness, studies of its neurophysiology will assume major importance.

Not all the research suggested in Section IV is highlighted in Table 5; for example, most of the suggestions on methodology and countermeasures appear only in Section IV. However, this does not imply that items not shown in the table are unimportant. Several matters that were considered worthy of special emphasis by the Working Group are reiterated here. One involves the desirability of exploiting the newer investigative methods of neuroscience when designing future experiments (see p.35, 37). Another is a need to develop alternate animal models, hopefully including species lower in the phylogenetic scale than cats, dogs, or monkeys, in which objective end points can be used for the study of space and motion sickness (see p.38). Such models may offer additional advantages

Table 5. Proposed Order of Priority of Research Suggested by the ad hoc Working Group on Space Motion Sickness*

STIMULUS-RESPONSE RELATIONSHIPS

- Delineate quantitatively the essential characteristics of the disorder with respect to environmental circumstances, symptomatology, and time course.
- Determine with certainity the indispensability of the vestibular apparatus as the key sensory element in space sickness.

REFLEX PATHWAYS

- Evaluate neuronal circuits in the vestibular nuclei and the vestibular centers of the cerebellum in mediating space and motion sickness and as a confirmation of the early experiments described by Tyler and Bard (1949).
- Confirm the role of the chemoreceptor trigger zone in the central emetic circuit.
- Explore meuronal elements of the vestibulo-cerebellar circuits for changes in electrophysiologic activity relating to habituation.
- Study the participation and functional specificity of chemical mediators at transmission points in the vestibulo-cerebellar-emetic circuit and possible modifying factors such as efferent input.
- Explore the relationship between space sickness and arousal mechanisms.
- Study interactions of vestibular and visual signals in the vestibular and cerebellar muclei as an approach to exploring the theories of sensory mismatch or conflict.
- Examine the interactions among vestibular, proprioceptive, visual, and somatosensory inputs recruited in the genesis of space sickness.

* Listed in order of decreasing priority in each of three categories shown. For detail, see Section V, A-F.

Table 5. (cont.)

RELATED VESTIBULAR NEUROPHYSIOLOGY

If the vestibular apparatus proves to be essential in the induction of space sicknes, the studies of its neurophysiology will assume major importance.

- Study the sensitivity of the semicircular canals to linear acceleration in the alert, chronic normal preparation, and relate this to space and motion sickness.

- Investigate in the alert preparation the relationship between afferent vestibular neuronal activity and efferent activity in situations in which the efferent system may participate.

- Explore circulatory factors regulating endolymph composition and function as these may affect vestibular function.

- Investigate the reported presence and functional significance of some species of postganglionic autonomic nerve fibers in various elements of the vestibular apparatus such as the vestibular nerve and terminals around vessels in the labyrinth.

- Identify and characterize at the single unit level, the afferent input from the vestibular organs resulting from complex motion stimuli such as cross-coupled accelerations.

in terms of availability and for possible large volume drug screening. The desirability of conducting studies in unanesthetized, alert animals was also noted.

There is a need to focus on studies of the cellular mechanisms in the peripheral end organs such as the mechano-electrical transduction process of hair cells and the biochemistry and neurophysiology of the adaptation mechanisms in the sensory neuroepithelium. Attention should be aimed, as well, at lower brain stem structures and final common pathways, perhaps via intensive studies of the vestibular cortex and vestibular thalamus in relation to space and motion sickness.

Finally, at the agency policy-making level, three suggestions of the Working Group should be highlighted. First, it might be appropriate to stage a recruiting drive to train the next generation of investigators for work in those disciplines that are germane to the study of space sickness. Second, the advisability should be considered of establishing an advisory group to continue the task of the present ad hoc Working Group on Space Motion Sickness until sufficient progress will have been made for satisfactory solution. And last, NASA should endeavor to improve its systems for wide and timely dissemination of biomedical data from its research programs, including the flight program. Increased publication in widely read scientific journals might be one objective.

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